Anaesthesia in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: retrospective analysis of a single centre three-year experience

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Abstract: BACKGROUND Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a treatment option for selected patients with peritoneal carcinomatosis. There are limited data available on anaesthesia management and its impact on patients' outcome. Our aim was to retrospectively analyze and evaluate perioperative management and the clinical course of patients undergoing CRS/HIPEC within a three-year period. METHODS After ethic committee approval, patient charts were retrospectively reviewed for patient characteristics, interventions, perioperative management, postoperative course, and complications. Analysis was intervention based. Data are presented as median (range). RESULTS Between 2009 and 2011, 54 consecutive patients underwent 57 interventions; median anaesthesia time was 715 (range 370 to 1135) minutes. HIPEC induced hyperthermia with an overall median peak temperature of 38.1 (35.7-40.2)°C with active cooling. Bleeding, expressed as median blood loss was 0.8 (0 to 6) litre and large fluid shifts occurred, requiring a total fluid input of 8.4 (4.2 to 29.4) litres per patient. Postoperative renal function was dependent on preoperative function and the type of fluids used. Administration of hydroxyethyl starch colloid solution had a significant negative impact on renal function, especially in younger patients. Major complications occurred after 12 procedures leading to death in 2 patients. Procedure time and need for blood transfusion were associated with a significantly higher risk for major complications. CONCLUSIONS Cytoreductive surgery with HIPEC is a high-risk surgical procedure associated with major hemodynamic and metabolic changes. As well as primary disease and complexity of surgery, we have shown that anaesthesia management, the type and amount of fluids used, and blood transfusions may also have a significant effect on patients' outcome.

DOI: https://doi.org/10.1186/1477-7819-12-136

Title

Anaesthesia in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: Retrospective analysis of a single centre three-year experience

Short title

Anaesthesia for CRS and HIPEC

Authors

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Abstract

Background.

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a treatment option for selected patients with peritoneal carcinomatosis. There are limited data available on anaesthesia management and its impact on patients' outcome. Our aim was to retrospectively analyse and evaluate perioperative management and clinical course of patients undergoing CRS/HIPEC within a three-year period.

Methods.

After ethic committee approval, patient charts were retrospectively reviewed for patient characteristics, interventions, perioperative management, postoperative course and complications. Analysis was intervention based. Data are presented as median (range).

Results.

Between 2009 and 2011, 54 consecutive patients underwent 57 interventions; median anaesthesia time was 715 (370-1135) min. HIPEC induced hyperthermia with overall median peak temperature of 38.1 (35.7-40.2) °C with active cooling. Median blood loss was 0.8 (0-6) l and large fluid shifts occurred, requiring total fluid input of 8.4 (4.2-29.4) l per case. Postoperative renal function was dependent on preoperative function and type of fluids used. Administration of hydroxyethyl starch colloid solution had a significant negative impact on renal function, especially in younger patients. Major complications occurred after 12 procedures leading to death

in 2 patients. Procedure time and need for blood transfusion were associated with a significantly higher risk for major complications.

Conclusions.

Cytoreductive surgery with HIPEC is a high-risk surgical procedure associated with major haemodynamic and metabolic changes. Besides primary disease and complexity of surgery, we could show that anaesthesia management, the type and amount of fluids used and blood transfusions have a significant effect on patients' outcome.

Keywords

Anaesthesia, General

Chemotherapy, Cancer, Regional Perfusion

Fluid Therapy

Hyperthermia, induced

Perioperative Care

Background

Over the last two decades, cytoreductive surgery combined with hyperthermic intraoperative chemotherapy (CRS/HIPEC) has become a therapeutic option for selected patients with peritoneal carcinomatosis [1]. Traditionally, peritoneal carcinomatosis was considered a palliative incurable condition [2]. Sugarbaker in 1995, however, first described that some of these patients may benefit from surgical removal of all macroscopic tumour combined with locoregional chemotherapy [3]. Since then, CRS/HIPEC has increasingly been used to treat patients with peritoneal carcinomatosis of different origin [4-11].

Strict patient selection is crucial and meticulous surgical tumour removal is mandatory for best clinical outcome [9, 12-14]. Thereby, long-time survival with good quality of life is feasible [15]. As there is a learning curve performing CRS/HIPEC, centralisation of the procedure to specialized institutions is recommended [16]. Regarding anaesthesia management and perioperative care, experience is limited and consensus has to be found yet [17]. Several authors have shown major changes in body temperature and haemodynamics, alterations in the composition of the blood as well as need for massive transfusion [18-21].

The aim of our study was to retrospectively analyse anaesthesia management and postoperative course of patients undergoing CRS/HIPEC over a 3-year period since introduction of this combined technique at the University Hospital Zurich.

Methods

After ethic committee approval (KEK: 2012-0174), all patients operated in a three-year period from 2009-2011 were included from a prospective database. Charts were retrospectively reviewed. There were no exclusion criteria. Fifty-four patients underwent 57 procedures. Data analysis was based on the number of procedures (57=100%).

Data collection and study variables

Anaesthesia and perioperative data were collected from electronic patient records (KISIM™, CISTEC AG, Zurich, Switzerland). Surgery was divided into three phases: CRS, HIPEC and reconstruction. Furthermore, we defined 6 particular time points in order to describe the course of the intervention (**Figure 1**). Data were collected on patient characteristics, anaesthesia, intraoperative fluid, transfusion and coagulation management, microcirculation and body temperature. Laboratory values and blood gas analysis were recorded until the second post-operative day. Additionally, post-operative course including complications according to the Clavien-Dindo classification were recorded, major complications including re-interventions under general anaesthesia (grade 3b), life-threatening complications requiring ICU management (grade 4) and death (grade 5) [22].

Cytoreductive surgery and HIPEC

All patients underwent extensive CRS followed by HIPEC. Peritonectomy was performed as described by Sugarbaker [3]. For HIPEC, the open abdomen technique, also referred to as the “coliseum technique”, was used, allowing the surgeons to manipulate abdominal content [23]. Inflow and outflow tubes were

connected to the hyperthermia pump (Belmont® Hyperthermia Pump, Belmont Instrument Corporation, Billerica, USA) and 750-1000 ml min^{-1} of pre-heated 1.5 % glucose peritoneal dialysis solution were circulated through the abdominal cavity. When target temperature of 41-42°C was reached, chemotherapeutic agents were added to the solution. Three different chemotherapeutic regimens were used: doxorubicin combined with either mitomycin or cisplatin and cisplatin combined with mitomycin. HIPEC was scheduled for 60 or 90 min; afterwards, the perfusate was drained and the abdominal cavity washed out with 4000 ml of normal saline (37°C). To prevent systemic hyperthermia, active cooling with forced air, cold packs and infusion of cold fluids (4°C) was used.

Anaesthesia and postoperative care

Anaesthesia was performed according to institutional guidelines with propofol or volatile anaesthetics with restrictive transfusion management and extensive haemodynamic monitoring. Combined anaesthesia including continuous thoracic epidural anaesthesia (TEA) was the technique of choice. After surgery, patients were transferred to the intensive care unit (ICU) or post-anaesthesia care unit (PACU). However, due to the lack of standardization at this early stage, individual management was up to the anaesthesiologist in care.

Guidance of vasopressor and fluid therapy

To prevent volume depletion, general fluid management included a continuous baseline infusion aiming at an urinary output of at least 2 ml kg^{-1} h^{-1}. If necessary, norepinephrine was applied continously in order to keep mean arterial blood pressure at baseline values. Arterial blood gas analyses were drawn to monitor signs of tissue

hypoperfusion such as decreasing pH and base excess or increasing serum lactate levels. Volume trials were initiated if urinary output was not achieved or signs of impaired microcirculation were present. If applicable, the PiCCO system [PULSION Medical Systems, Munich, Germany] was used for goal-directed haemodynamic and fluid management. In steady state, with surgical manipulation absent, parameters of transpulmonary thermodilution and of pulse-contour analysis were acquired: Stroke volume variation of higher than 10% was inerpreted as a marker for volume responsiveness. Changes in cardiac output, global end-diastolic volume and extravascular lung water indexes were monitored and used as markers for further volume trials or vasopressors according to the manufacturer's haemodynamic decision model (www.pulsion.com/international-english/academy/download-center/english/picco).

Statistical methods

Data were extracted from patient records and stored in an Excel File (Microsoft Office 2011). Descriptive statistics are presented as median and ranges for continuous variables and as counts for categorical variables. Intraoperative changes of body temperature, heart rate, mean arterial blood pressure (MAP) and central venous pressure (CVP) were addressed separately with mixed effects models, accounting for repeated observations over time, and adjusting for the potential confounders age, gender, and body mass index (BMI). The box-cox-transformed glomerular filtration rate (GFR) measured postoperatively (day 1 and 2) was modelled with multiple linear regression. Independent factors were preoperative GFR, blood loss, urine output and different intravenous fluid preparations (Supplementary data, **Table S1**). For binary

outcomes such as postoperative ventilation and major (≥3b) complications, multiple logistic regression models were used. Independent factors are shown in **Table S2.** Resulting effect sizes correspond to the logarithm of the odds ratios (OR).

The fentanyl consumption per kg body mass, length of postoperative ventilation, time to first bowel passage and the length of stay on the ICU between the groups of patients with and without additional thoracic epidural anaesthesia (TEA) were compared with a non-parametric Wilcoxon test (**Table S3**). P-values < 0.05 were considered statistically significant.

All statistical procedures ignored the fact that three patients had two HIPEC interventions, and observations were considered independent. All analyses were performed with R. [24] For descriptive statistics the package reporttools was used, for fitting the random effects models, package lme4 was used. Details of statistical analyses are presented as supplementary data (**Table S1-3**).

Results

Data on patient characteristics and primary cancer are presented in **Table 1**. Fifty-four patients underwent 57 interventions. Median BMI was 25 (16-41). The majority of patients suffered from cancer originating from the vermiform appendix. Other primary tumour localizations included colorectal and gastric cancer, mesothelioma, endometroid and ovarian cancer and cancer arising from urachus and small intestine. Median operation time was 550 (255-995) min and median anaesthesia time was 715 (370-1135) min. Median time for CRS was 340 (95-790) min, for HIPEC 90 (60-115) min and for reconstruction 119 (40-237) min.

Anaesthesia and Monitoring

Data on intra- and perioperative parameters are presented in **Table 2**. Besides routine monitoring, advanced haemodynamic monitoring was used in 91% of all procedures (PiCCO [PULSION Medical Systems, Munich, Germany] n=48; pulmonary artery catheter [Swan-Ganz CCOmbo, Edwards Life Sciences, Unterschleissheim, Germany] n=3; both techniques n=1). General anaesthesia was performed according to institutional standards, 79% (n=45) were combined with a continuous thoracic epidural anaesthesia (TEA, ropivacaine 0.33% 6-12 ml h^{-1}). Anaesthesia was maintained with propofol (n=37), sevoflurane (n=17) or desflurane (n=3) and supplemented with intravenous fentanyl according to patients' needs. Overall median fentanyl consumption was 1.2 (range 0.2-4.0) mg. Postoperatively, thoracic epidural anaesthesia was maintained with ropivacaine 0.2% at a rate of 6-15 ml h^{-1}.

Body temperature and haemodynamics

HIPEC induced hyperthermia with median overall peak temperature of 38.1 (35.7-40.2) °C. Body temperature changed significantly over time (**Figure 2A**).

The following haemodynamic changes were found (data not shown): Heart rate significantly increased throughout the procedure, peaking at the end of HIPEC, and remained high until the end of surgery. Mean arterial blood pressure was kept within 10% of baseline. Norepinephrine was administered in 55 patients with median overall peak doses of 7 (0.5-30) µg min^{-1}. Median central venous pressure (CVP) increased significantly during the first part of the operation (H0-H2).

Fluid and coagulation management

Detailed information on intraoperative fluid, transfusion and coagulation management is shown in **Table 3**. Coagulation parameters were analysed using routine laboratory testing and bedside thromboelastography (ROTEM®, Tem Innovations GmbH, Munich, Germany). One patient suffering from a known hereditary factor VII deficiency required recombinant factor VIIa. Postoperatively, 7 patients showed thrombocytopenia (<50000 $µl^{-1}$) and 9 patients developed leukocytopenia (<4000 $µl^{-1}$) on median postoperative day 3 (0-12). Pre-operative hemoglobin values were 127 (97-164) g l^{-1}, falling to a minimum of 82 (46-125) g l^{-1} intraoperatively. At the end of surgery, median haemoglobin level was 92 (range 59-128) g l^{-1} and remained low until postoperative day 2.

Renal function and metabolic alterations

Details on urine output are summarised in **Table 3**. To maintain urine output during HIPEC, fluids in combination with IV diuretics were given in 35 patients (61%).

Furosemide was administered in 25 patients (44%), mannitol was given in 20 patients (35%) and 10 patients (18%) received both drugs. Median doses were 10 (2.5-20) mg for furosemide and 20 (20-40) g for mannitol. Two patients became oliguric (urine output < 0.5 ml kg^{-1} h^{-1}) without clinical relevance. Preoperative glomerular filtration rate (GFR) had an impact on postoperative GFR: The higher the pre-operative value, the higher the post-operative value ($p<0.001$) (**Table S1**). Intraoperative blood loss and urine output had no significant impact on postoperative GFR (**Table S1**). Regarding the type of fluid administered, we did not find any negative effects of crystalloids on renal function. However, the amount of hydroxyl-ethyl starch (HES) given had a significant negative effect on postoperative GFR in patients younger than 60 years ($p<0.001$) (**Table S1**). Three patients (5%) suffered from acute deterioration of renal function during their hospital stay.

During surgery, pH and base excess (BE) decreased significantly. Lowest values were reached at the end of HIPEC (H3) with median pH of 7.38 (7.27-7.53) and median BE of -4.3 (-10.8-0.6) mEql l^{-1}. **Figure 2B** describes plasma lactate levels inversely increasing throughout the intervention. Hyperglycaemia, defined as a blood glucose level of > 10 mmol l^{-1}, was present in 42 patients (74%). Sixteen patients (28%) required insulin therapy intraoperatively, only one of the patients was a known diabetic.

Post-operative course

Median hospital stay was 17 (9-259) days and median length of ICU stay was 2 (1-35) days. Thirty-three ICU patients were ventilated on ICU arrival. The more opioids given intraoperatively, the higher was the probability for postoperative mechanical ventilation ($p<0.05$, **Table S2**). The overall duration of surgery ($p<0.001$, **Figure 3A**)

and the amount of blood loss ($p<0.05$, **Figure 3B**) had a significant impact on the need for mechanical respiratory support (**Table S2**). Comparing post-operative course of patients with and without TEA, we found a significant difference in the amount of fentanyl given: Patients with combined anaesthesia needed less fentanyl ($p<0.001$). We could not show any difference in the length of post-operative ventilation ($p=0.56$), length of stay on the ICU ($p=0.52$) nor time to first bowel passage ($p=0.73$) between the two groups (**Table S3**). However, the sample was strongly unbalanced, as sample sizes in the two groups were very different and data were missing. Regarding anaesthesia-related complications, one patient developed an epidural abscess after TEA, requiring operative decompression 7 days after insertion.

Major surgical complications (≥3b)

Major complications according to the Clavien-Dindo classification (grade 3b-5) [22] occurred after 12 interventions, two patients (4%) died. The *first* patient, a 46-year old man, was suffering from adenocarcinoma of the oesophagogastric junction and underwent transhiatal oesophagogastrectomy. Effective operation time was 800 min. The patient required 8 units of PRBC, 500 IU prothrombine complex concentrate (PCC) and 10 g fibrinogen due to extensive bleeding (lowest haemoglobin 47 g l^{-1}) intraoperatively. After an uneventful initial recovery, the patient died 17 days later from haemorrhagic shock and multiorgan dysfunction syndrome. The *second* patient, a 57-year old man, was suffering from a mucinous adenocarcinoma of the appendix with peritoneal carcinomatosis. Effective operation time was 995 min. Surgery was complex and the patient required 4 units of PRBC (lowest haemoglobin 71 g l^{-1}), one unit of platelets and several coagulation factor concentrates (14 g fibrinogen, 2500 IU

factor XIII, 1000 IU PCC and 1000 IU factor VIII). After a long postoperative course with several re-interventions the patient died after 259 days from septic shock.

The rate of major surgical complications increased significantly with longer operation (**Figure 3C)** and anaesthesia time (both $p<0.01$; **Figure 3D**, **Table S2**). We found blood transfusion to be an independent risk factor for major complications ($p<0.05$; **Table S2**). The lowest overall haemoglobin values (describing the amount of blood loss) correlated with a trend towards an increased risk of major complications ($p=0.05$, **Table S2**). The administration of coagulation factor concentrates did not increase the risk of major complications nor did the presence of obesity, arterial hypertension, carcinoma of the appendix or pre-operative anaemia (**Table S2**).

Discussion

Data on anaesthesia management and outcome of 57 consecutive patients undergoing combined CRS/HIPEC were retrospectively collected and analysed at our hospital. Besides the surgical complexity of the individual case, we could show that several factors affect patients' outcome, i.e. type and amount of resuscitation fluids used, as well as blood transfusions.

Cytoreductive surgery with HIPEC is a long-lasting, abdominal surgical procedure (median anaesthesia time 715 min) with additional hyperthermia and intraoperative chemotherapy. Extensive bleeding and fluid shifts may occur. Therefore, fluid status and cardiac function were continuously assessed with advanced haemodynamic monitoring in most of our patients.

Currently the type and amount of fluid administration are subject of debate [25-27]. Our fluid management consisted of both, crystalloids and colloids: Besides crystalloids, 51 patients received gelatine and 14 were given HES additionally, in a ratio of approximately 2.5:1. At the time of observation, studies on potential harmful effects of HES preparations in septic ICU patients had not been published so far [28, 29]. Our data are in accordance with these publications: HES administration had a significant negative impact on renal function, especially in younger patients.

Maintaining renal function and prevention of injury is critical for best perioperative outcome [30]. Known risk factors for acute renal injury are hypovolaemia, hypotension, major surgery, nephrotoxic drugs, blood transfusions and systemic inflammation [31]. Haemodynamic optimisation (i.e. optimising cardiac output, tissue perfusion and oxygenation) is highly recommended to prevent renal injury: The goal is to maintain the effective circulating blood volume by careful fluid and transfusion management, vasopressors and inotropics [32]. Most authors recommend liberal fluid

regimens [14, 18, 33]. Our patients received approximately 10 ml kg^{-1} hr^{-1} of fluids and lost 3 ml kg^{-1} hr^{-1} (**Table 3**). The amount of fluids given was guided by haemodynamic parameters, blood gas analyses and urinary output. Most patients were given vasopressors to maintain MAP and, although the benefit of its application is questionable, 35 patients were given IV diuretics to force diuresis during HIPEC [32]. In fact, there is no evidence for a single pharmacological intervention during surgery to protect the kidneys from damage [30, 34].

Our data suggest that the need for blood transfusion is associated with an increased risk for major complications (grade ≥3b according to Clavien-Dindo score [22]). The amount of bleeding showed a trend towards major complications (p=0.05). It is standard procedure for both, the surgical and the anaesthesia team, to assess and estimate blood loss at the end of surgery. However, differences between both estimates result in inconsistent documentation. Alternatively, the decrease in haemoglobin concentration can be used as an indicator for blood loss: Both methods are widely used in clinic but are known to be of limited accuracy tending to underestimate actual blood loss [35]. For future studies it might be useful to refer to a superior, validated blood loss score taking into account the haemoglobin concentration of suction fluid [35].

Exposure to blood transfusions is associated with increased morbidity and mortality in surgical oncology [36, 37]. It is therefore critical to control surgical bleeding and to diagnose and correct coagulopathy early. Goal-directed, aggressive treatment using algorithms and point-of-care coagulation testing is recommended [36]. In our study, 28% of patients required intraoperative blood transfusions and 37% of patients were given coagulation factor concentrates. In contrast to others, routine FFP administration is not the first-line treatment for established coagulopathy at our

institution [17]. Only 5% of patients received FFPs compared to 45% described in the literature [17, 18]. The pathophysiology of coagulopathy in patients undergoing CRS/HIPEC is not completely understood [14, 17]. Besides bleeding, consumption and dilution, patients are exposed to extreme changes in body temperature, both hypo- and hyperthermia, suffer from metabolic acidosis and calcium depletion (40% of our patients required calcium supplementation).

The use of TEA is recommended for patients undergoing CRS/HIPEC to provide optimal pain therapy, to reduce length of postoperative ventilation and pulmonary complications and to allow early mobilisation [14, 33]. Critics underline the potential risk of haemodynamic instability, epidural haematoma and infectious complications due to massive bleeding, impaired coagulation and chemotherapy-induced immunodeficiency [38-40]. Recently an incidence for infectious complications of 1:2139 has been reported [17]. One of our patients suffered from epidural abscess with need for operative decompression 7 days after placement. To prevent infections we recommend to limit the postoperative use of epidural analgesia to a maximum of 5 days and to daily visit patients with TEA. Despite the frequent use of TEA, only 28 % of CRS/HIPEC centres describe their pain management as excellent [17]. Most of our patients received TEA for intra- and post-operative analgesia and we found a significant opiod sparing effect. However, unlike previous publications, we could not show that TEA was associated with reduced length of post-operative ventilation and ICU-stay, nor shortened time to first bowel passage [18].

The present observational study has some limitations. The anaesthesia management of patients did not follow strict protocols and there were no pre-defined exclusion criteria to the study. Furthermore data were collected retrospectively and some data

were missing due to absent documentation, compromising data analysis and reducing power of statistical conclusions.

Conclusion

Taken together, combined CRS/HIPEC is a high-risk surgical procedure associated with major haemodynamic and metabolic changes. It requires coordinated and patient-centred anaesthetic management, including meticulous monitoring of the different physiological systems of the body. Besides primary disease and complexity of surgery, we could show that the type and amount of fluids used, transfusions and anaesthetic management have an impact on patients' outcome. To further differentiate factors affecting the outcome prospective, randomized, controlled trials are highly warranted in this field.

Competing interests

The authors declare that they have no competing interests.

Funding

This study has been funded through institutional support only.

Author's contribution

MT.G. initiated, planned and designed the study. MT.G. and ME.K. obtained ethic committee approval. ME.K. was responsible for data collection and analysis. R.K and U.H. performed statistical analyses and revised the manuscript. K.L. was involved in data acquisition and patient recruitment. ME.K. wrote the first draft of the paper. MT.G. and B.BS revised the manuscript. All authors have approved the final version.

Acknowledgements

The authors would like to thank Sereina Graber for statistical support.

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Table 1: Patient characteristics, primary cancer and intraperitoneal chemotherapy

Age; years	52 (20-72)
Gender; M:F	23:34
Weight; kg / **Height;** cm	70 (44-112) / 168 (155-185)
Body Mass Index; kg m^{-2}	25 (16-41)
ASA class I/II/III	5/49/3
Co-Morbidities [1]	
Cardiovascular	14
Pulmonary	5
Renal	4
Endocrine	3
Neurological	4
Obesity (BMI>30)	8
Medication	
Single ß-blocking agent	2
Single ACE-Inhibitor/AT1-Blocker	3
Single diuretic	0
Combination of at least two drugs	6
Other drugs[2]	27
None	23
Origin of primary cancer	
Appendix	33
Ovary	1
Colorectal	13
Mesothelioma	5
Gastric	1
Other origin[3]	4

54 patients underwent 57 procedures. Data are expressed as median (range) and numbers.

ASA=American Society of Anesthesiology, BMI= body mass index (kg m^{-2}), ACE=angiotensin converting enzyme, AT=angiotensin

[1] Co-morbidities: *cardiovascular* (arterial hypertension, cardiac valve pathology, hyperlipidaemia); *pulmonary* (chronic bronchitis, asthma, obstructive sleep apnoe syndrome, history of acute respiratory distress syndrome, history of pulmonary embolism); *renal* (one sided kidney agenesia, history of carcinoma of the kidney, incidentaloma, chronic kidney disease); *endocrine* (previous ovarectomy, medically

treated hypothyroidism, diabetes mellitus); *neurological* (polyneuropathy, paraesthesia, migraine, herniated vertebral disc with neurological symptoms).

[2] Twenty seven patients were on additional medication: analgesics (n=9), proton pump inhibitors (n=6), vitamins and supplements (n=5), laxatives (n=5), hormone replacement therapy (n=5), sedatives (n=3), oral antidiabetics (n=1), chemotherapeutic agents (n=1), antidepressants (n=1), antidiarrheals (n=1), antiemetics (n=1), ASS (n=1), statins (n=1), calcium channel blocker (n=1), herbal and homeopathic preparations (n=2).

[3] Other origin summarizes endometroid cancer (n=2), cancer of the small intestine (n=1) and urachus cancer (n=1).

***Table 2*: Intra- and perioperative parameters**

Anaesthesia time; min	715 (370-1135)
Additional thoracic epidural anaesthesia	45
Advanced haemodynamic monitoring	
PiCCO	48
Pulmonary artery catheter	3
both	1
Anaesthesia maintainance	
Propofol	37
Sevoflurane	17
Desflurane	3
Cumulative fentanyl dose; mg	1.2 (0.2-4.0)
Effective operation time; min	550 (255-995)
Length of CRS; min	340 (95-790)
Length of HIPEC, min	90 (60-115)
Length of reconstruction; min	119 (40-237)
Intraperitoneal chemotherapy (mg m^{-2})	
Doxorubicin/Mitomycin (15/15)	49
Doxorubicin/Cisplatin (15/50)	6
Cisplatin/Mitomycin (17/10)[1]	2
Transfer to ICU	53
Length of ICU stay; d	2 (1-35)
Postoperative ventilation	33
Length of postoperative ventilation; hours[2]	4 (1-10)
Hospital stay; d	17 (9-259)

Data presented as median (range) or numbers (n).

CRS = Cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy, ICU = Intensive care unit

Haemodynamic monitoring: PiCCO [PULSION Medical Systems, Munich, Germany]; Pulmonary artery catheter [Swan-Ganz CCOmbo, Edwards Life Sciences, Unterschleissheim, Germany]

[1] Reduced dose of cisplatin was given in n = 2 patients.

[2] Data missing in n = 6 patients

***Table 3*: Perioperative fluid balance, blood loss and substitution**

	n	Median (range)
Input		
Fluids		
Crystalloids; ml	57	5900 (2200-19100)
Crystalloids per hour; ml h^{-1}		473 (187-1041)
Colloids; ml	56	2500 (500-14500)
Colloids per hour; ml h^{-1}		189 (52-852)
HES 130/0.4; ml	14	1000 (500-2500)
Gelatine; ml	51	2500 (500-12000)
Blood products and coagulation factor concentrates		
PRBC; n	16	4 (1-10)
FFP; n	3	6 (4-8)
Thrombocytes; n	4	1 (1-2)
Fibrinogen; g	21	4 (2-22)
Prothrombine Complex Concentrate; IE	9	1000 (400-2000)
Factor XIII; IE	13	1500 (1250-4000)
Factor VIII-vWF; IE	1	1000
Recombinant Factor VII; µg	1	1000
Total input; ml	57	8200 (4200-29400)
***Total hourly input;* ml h^{-1}**		697 (363-1603)
Output		
Blood loss; ml	57	800 (0-6000)
Urine; ml	57	1460 (330-3970)
Urine per hour, CRS; ml h^{-1}		94 (34 -350)
Urine per hour, HIPEC; ml h^{-1}		220 (47-787)
Urine per hour, Reconstruction; ml h^{-1}		183 (33-631)
Ascites; ml	11*	1500 (100-3000)
Total output; ml	57	2670 (530-10780)
***Total hourly output;* ml h^{-1}**		218 (58-729)

54 patients underwent 57 procedures. Data are expressed as median (range) and numbers (n).

HES = hydroxyethyl starch, PRBC = packed red blood cells, FFP = fresh frozen plasma, vWF = von Willebrand factor

Fluids: Crystalloids = Ringerfundin® (B.Braun Medical AG, Melsungen, Germany); Colloids = gelatine (Physiogel® balanced, B. Braun Medical AG, Melsungen,

Germany) and HES 130/0.4 (Tetraspan®, B. Braun Medical AG, Melsungen, Germany). PRBC and thrombocytes were applied in units of 300 ml, FFP in units of 280 ml.

Coagulation factor concentrates: Fibrinogen (Hemocomplettan P®, CSL Behring AG, Bern, Switzerland), Prothrombin complex concentrate (PCC, Beriplex P/N®, CSL Behring AG, Bern, Switzerland), Factor XIII (Fibrogammin P®, CSL Behring AG, Bern, Switzerland), Factor VIII-vWF (Hemate P®, CSL Behring AG, Bern, Switzerland), recombinant Factor VIIa (Novoseven®, Novo Nordisk Pharma AG, Kusnacht, Switzerland).

*data missing in 46 patients

Figure legends

Figure 1: **Time course of procedure.**

HIPEC = hyperthermic intraperitoneal chemotherapy, baseline = after induction of anaesthesia but 5 minutes before start of the operation, H0 = 30 min before HIPEC, H1 and H2 = 30 and 60 min after start of HIPEC, H3 = end of HIPEC, End = 5 minutes before end of the operation.

Figure 2: **Intraoperative course of temperature and lactate.**

A. Change in temperature compared to baseline: the horizontal line set at 0 is representing baseline. If the 95% confidence interval presented for each time point does not overlap with baseline, temperature differs significantly from baseline ($p<0.05$). A mixed effect model describing the effect of phase was used.

B. Boxplot describing arterial lactate levels throughout the intervention

Baseline = after induction of anaesthesia but before start of the operation, H0 = 30 minutes before HIPEC, H1 and H2 = 30 and 60 minutes after start of HIPEC, H3 = end of HIPEC, End = 5 minutes before end of the operation.

Figure 3: **Operation time, blood loss and anaesthesia time and their effects on the need for post-operative ventilation and major surgical complications.**

A and **B**. The multiple logistic regression model describes the need for postoperative respiratory assistance (vertical axis: 0 = no assistance, 1 = assistance needed) depending on operation time (minutes) and blood loss (ml). The longer the operation

($p<0.01$) and the higher the blood loss ($p<0.05$), the higher was the need for postoperative ventilation.

C and **D**. Major complications (≥ 3b according to the Clavien-Dindo-classification; for details please refer to the text) on the vertical axis (0 for complications < 3b, 1 for ≥ 3b) are plotted against operation time (minutes) or anaesthesia time (minutes) on the horizontal axis. The longer the operation ($p<0.01$) and the longer anaesthesia time ($p<0.01$), the higher was the incidence of major complication.

Data are corrected for BMI and age.

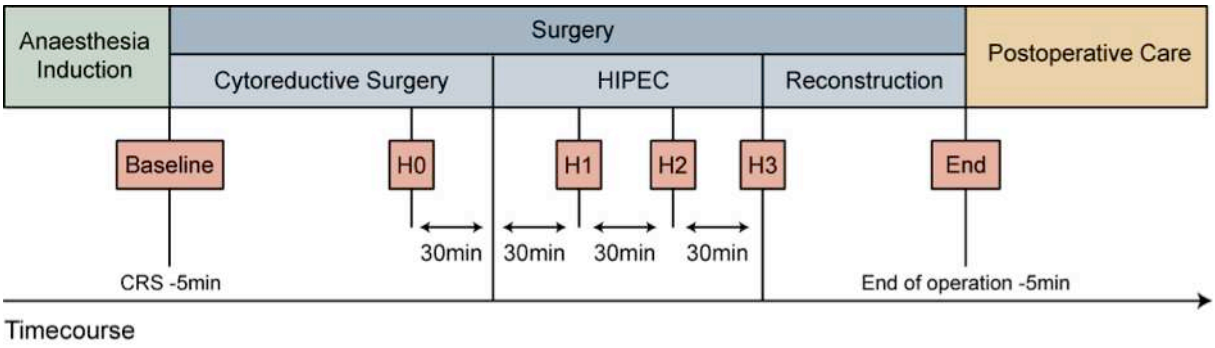

Figure 1

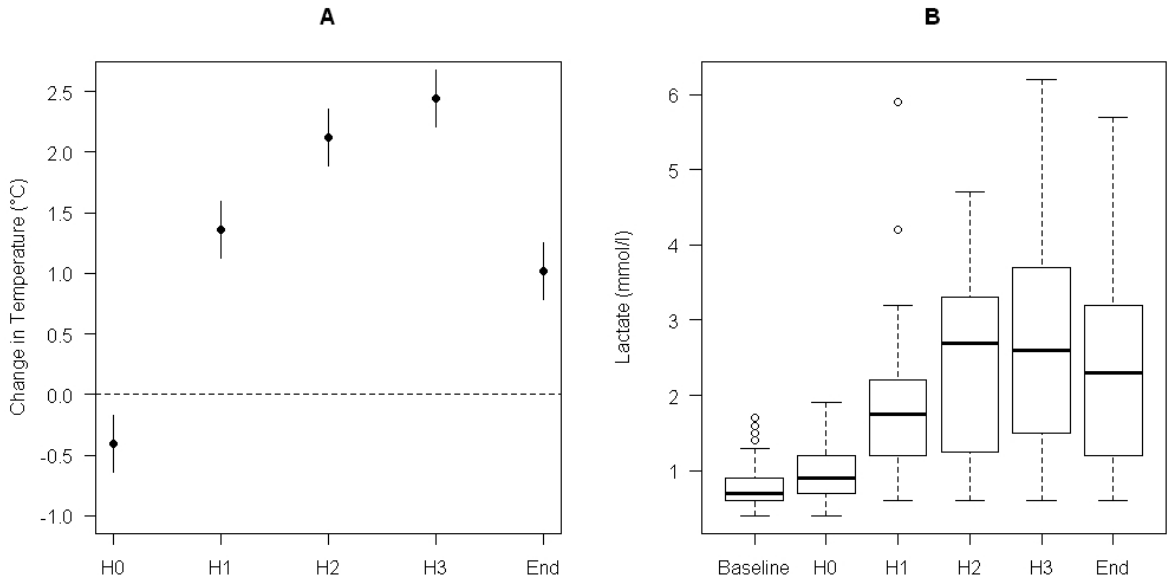

Figure 2

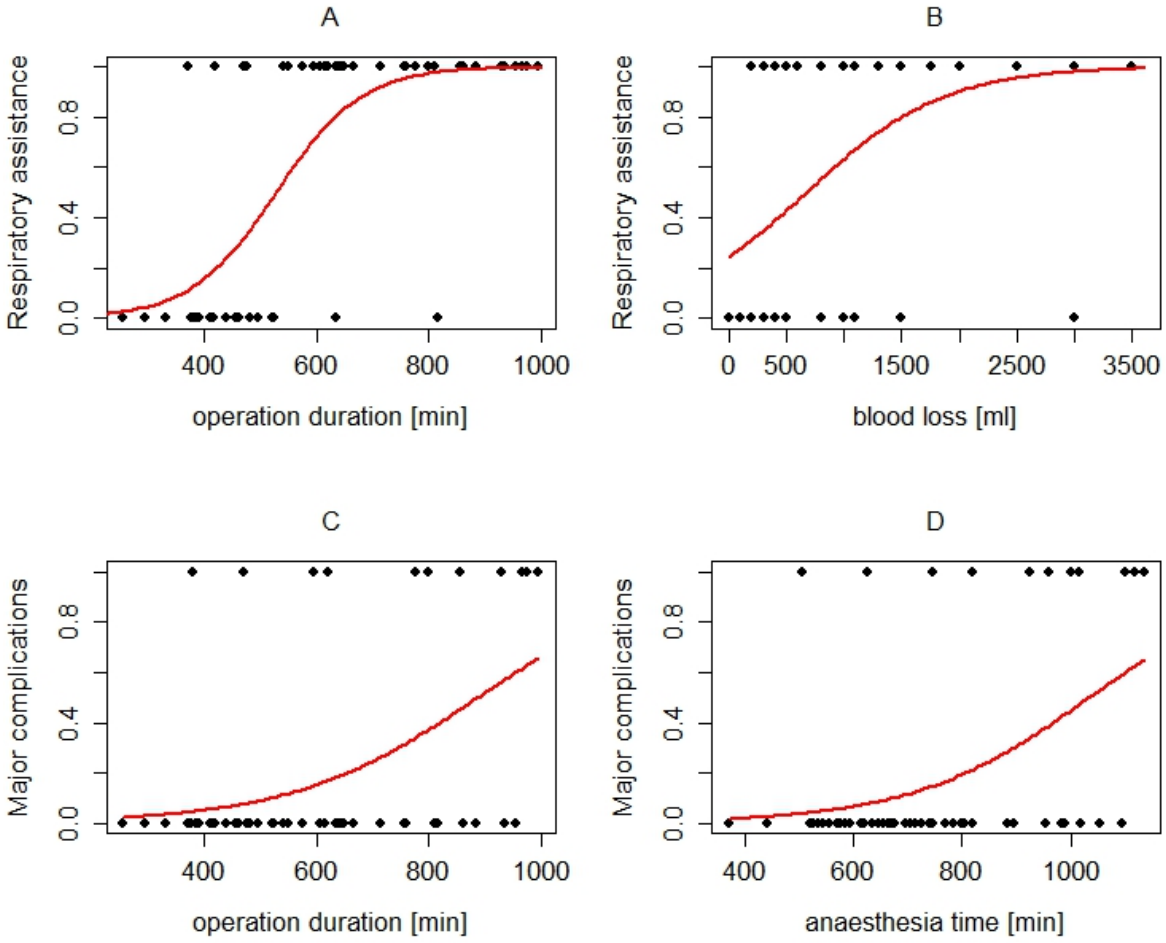
A
Respiratory assistance
0.0
0.4
0.8
400
600
800
1000
operation duration [min]
B
Respiratory assistance
0.0
0.4
0.8
0
500
1500
2500
3500
blood loss [ml]
C
Major complications
0.0
0.4
0.8
400
600
800
1000
operation duration [min]
D
Major complications
0.0
0.4
0.8
400
600
800
1000
anaesthesia time [min]

Figure 3

***Table S 1*: Multiple linear regression models**

Multiple linear regression model				
Dependent variable	**Independent variable**	**Effect size**	**Standard error**	**p-value**
GFR postoperative day 1*	Preoperative GFR	0.729	0.154	**<0.001**[1]
	Age	-0.118	0.255	0.645
	BMI	-0.204	0.455	0.656
GFR postoperative day 2*	Preoperative GFR	0.809	0.155	**<0.001**[1]
	Age	0.198	0.257	0.445
	BMI	-0.184	0.459	0.69
GFR postoperative day 1*	Intraoperative blood loss	-0.001	0.002	0.75
	Age	-0.131	0.26	0.618
	BMI	-0.202	0.459	0.663
	Preoperative GFR	0.725	0.155	**<0.001**[1]
GFR postoperative day 2*	Intraoperative blood loss	<-0.001	0.002	0.884
	Age	0.192	0.267	0.468
	BMI	-0.183	0.463	0.695
	Preoperative GFR	0.807	0.157	**<0.001**[1]
GFR postoperative day 1*	Intraoperative urine secretion per time	-1.547	2.454	0.531
	Age	-0.128	0.257	0.620
	BMI	-0.214	0.458	0.643
	Preoperative GFR	0.732	0.155	**<0.001**[1]
GFR postoperative day 2*	Intraoperative urine secretion per time	1.254	2.477	0.615

	Age	0.206	0.26	0.431
	BMI	-0.176	0.462	0.705
	Preoperative GFR	0.806	0.156	**<0.001**[1]
GFR postoperative day 1*	Amount of cristalloids given over time (ml min^{-1})	-0.014	0.715	0.984
	Age	-0.118	0.258	0.649
	BMI	-0.204	0.46	0.659
	Preoperative GFR	0.729	0.155	**<0.001**[1]
GFR postoperative day 2*	Amount of cristalloids given over time (ml min^{-1})	-0.768	0.713	0.286
	Age	0.175	0.258	0.499
	BMI	-0.187	0.458	0.685
	Preoperative GFR	0.813	0.155	**<0.001**[1]
GFR postoperative day 1*	Age*amount of HES given over time (ml min^{-1})	0.949	0.204	**<0.001**[1]
	Age	-0.56	0.236	**0.022**[1]
	BMI	-0.411	0.39	0.297
	Preoperative GFR	0.805	0.132	**<0.001**[1]
	Amount of HES given over time	-52.54	11.124	**<0.001**[1]
GFR postoperative day 2*	Age*amount of HES given over time (ml min^{-1})	0.95	0.204	**<0.001**[1]
	Age	-0.245	0.236	0.305
	BMI	-0.375	0.39	0.341
	Preoperative GFR	0.882	0.132	**<0.001**[1]
	Amount of HES given over time	-53.906	11.116	**<0.001**[1]
Amount of transfused PRBC	Preoperative anemia (Hb<117g l^{-1})	-0.096	0.448	0.832
	Age	-0.001	0.015	0.956
	BMI	0.012	0.031	0.7

GFR = Glomerular filtration rate, BMI = body mass index (kg m^{-2}), HES = hydroxyethyl starch, PRBC = packed red blood cells

[1]Statistically significant

*box-cox-transformed

Table S2: **Multiple logistic regression models**

Multiple logistic regression model				
Dependent variable	**Independent variable**	**Effect size**	**Standard error**	**p-value**
Postoperative ventilation	Amount of opiods (mg)	0.919	0.391	**0.018**[1]
	Age	0.016	0.028	0.576
	BMI	-0.006	0.06	0.925
Postoperatve ventilation	Overall duration of operation (min)	0.014	0.004	**<0.001**[1]
	Age	0.043	0.043	0.316
	BMI	0.015	0.076	0.84
Postoperative ventilation	Blood loss (ml)	0.002	0.001	**0.003**[1]
	Age	0.008	0.029	0.782
	BMI	0.02	0.064	0.749
Complications ≥ 3b	Operation time (min)	0.006	0.002	**0.004**[1]
	Age	-0.03	0.042	0.48
	BMI	-0.075	0.087	0.391
Complications ≥ 3b	Anaesthesia time (min)	0.006	0.002	**0.005**[1]
	Age	-0.031	0.042	0.46
	BMI	-0.077	0.087	0.379
Complications ≥ 3b	Lowest intraoperative haemoglobin value (g l^{-1})	-0.037	0.019	0.054
	Age	-0.048	0.034	0.157
	BMI	-0.052	0.08	0.515
Complications ≥ 3b	Blood transfusion (0/1)	1.76	0.724	**0.015**[1]

	Age	-0.038	0.034	0.268
	BMI	-0.075	0.082	0.359
Complications ≥ 3b	Coagulation factor (0/1)	1.159	0.69	0.093
	Age	-0.044	0.034	0.192
	BMI	-0.066	0.081	0.414
Complications ≥ 3b	Obesity (BMI>30 kg m^{-2})	0.128	1.6	0.936
	Age	-0.042	0.032	0.188
	BMI	-0.072	0.106	0.501
Complications ≥ 3b	Hypertension	0.778	1.082	0.472
	Age	-0.049	0.034	0.148
	BMI	-0.094	0.089	0.29
Complications ≥ 3b	Carcinoma of the appendix	0.1	0.685	0.886
	Age	-0.042	0.032	0.186
	BMI	-0.067	0.077	0.38
Complications ≥ 3b	Pre-operative anaemia (Hb<117g l^{-1})	1.19	0.872	0.173
	Age	-0.048	0.032	0.129
	BMI	-0.08	0.078	0.313

[1]Statistically significant

BMI = body mass index (kg m^{-2}), Hb = haemoglobin concentration (g l^{-1})

***Table S 3*: Wilcoxon rank sum tests**

Wilcoxon rank sum tests				
Dependent variable	**Groups**	**N**	**Mean**	**p-value**
Fentanyl given intraoperatively (mg) n=57	Additional TEA versus no additional TEA	n=45 versus n=12	0.015 versus 0.03471854	<0.001[1]
Length of postoperative ventilation (h) in n=27** patients	Additional TEA versus no additional TEA	n=20 versus n=7	5.013 versus 4.536 hours	0.560
Total stay on ICU (days) in n=53 patients	Additional TEA versus no additional TEA	n=42 versus n=11	3.024 versus 1.545 days	0.519
Time to first bowel passage (days) in n=55 patients***	Additional TEA versus no additional TEA	N=44 versus n=11	5.3409 versus 5.7272 days	0.732

[1]Statistically significant

**data missing in n=6 patients

*** data missing in n=2 patients

TEA = thoracic epidural anaesthesia, ICU = intensive care unit